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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/537,088	03/29/00	DWIVEDI	A 82239

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EXAMINER	
RUSSEL, J	
ART UNIT	**PAPER NUMBER**
1653	4

DATE MAILED:
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (REV. 2/95)

1-File Copy

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Office Action Summary

Application No.	Applicant(s)
09/527,088	A. Dwivedi et al
Examiner	**Group Art Unit**
J. Russel	1653

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 3-29-2000.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-15 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 1-15 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons:

The amino acid sequence at page 3, line 3, of the specification is subject to the sequence disclosure rules, but no sequence listing has been submitted. Further, a SEQ ID NO needs to be inserted after each occurrence of a sequence subject to the sequence disclosure rules. See 37 CFR 1.821(d).

Applicant must provide an original computer readable form (CRF) copy of the Sequence Listing, an original paper copy of the Sequence Listing as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter as required by 37 CFR 1.825(a) and (b).

2. The disclosure is objected to because of the following informalities: Because of insufficient top margins, the first lines of pages 3, 9, 11, and 12 were partially obliterated by hole punching. These lines of the specification will have to be re-submitted by appropriate amendment. Because of poor copy quality, at least portions of page 1, line 21, and page 8, line 1, are illegible. These lines of the specification will have to be re-submitted by appropriate amendment. There is no Brief Description of the Drawings as required by 37 CFR 1.74. At page 1, line 7, there is an incomplete sentence (i.e., "Dimethyl-beta cyclodextrin."). At page 1, line 14, "analgesics" is misspelled. At page 2, lines 12 and 13, there are unmatched beginning brackets. At page 4, line

1, the inverted numeral "4" should be deleted. At page 6, line 4, "hydroxyethyl" should be deleted. At page 13, line 20, commas should be inserted after "brain" and "heart". There is an unmatched end parenthesis at page 13, line 14. At page 13, last line, there is an unmatched beginning parenthesis. At page 14, line 19, it is believed that "peat" should be "peak". The heading "TABLE 4" should be inserted above the table at page 16, lines 3-4. At page 17, line 1, it is believed that "tritan" is a misspelling of "Triton". Also, Applicants are reminded of the necessity of capitalizing all trademarks and including generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. The specification would benefit from further grammatical revision. Appropriate correction is required.

3. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 requires "significantly improved oral efficacy and prolonged duration" but does not provide any basis to determine whether or not oral efficacy is improved and duration is prolonged. It is not clear with respect to what pharmaceutical formulation or formulations Applicants' complexes are to be compared. Claim 1 uses Markush terminology, i.e. "selected from the group consisting of', which is used to set forth alternative choices, but claim 1 does not set forth any alternatives. The peptide and the cyclodextrin are not alternatives to each other, but rather are to be used in combination. In claim 1, the phrase "highly potent" is indefinite because

"highly" is a relative term, but no standard of reference has been provided with which to determine whether or not the opioid peptide is "highly potent" or not. Because the opioid peptide is specifically defined in the claim, it may be that the phrase "highly potent" is redundant and could be deleted without affecting the scope of the claim. Claims 8, 14, and 15 recite an inclusion complex of the opioid peptide "with beta-cyclodextrin as claimed in claim1". However, claim 1, is not limited to beta-cyclodextrin, but embraces the use of any cyclodextrin derivative, and it is not clear if claims 8, 14, and 15 were intended to be limited just to beta-cyclodextrin. Claim 10 recites the composition "formulated in various physical forms". It is unclear if this claim requires the simultaneous presence of various physical forms, i.e., it is not clear if the composition in a single physical form is embraced within the scope of the claim. At claim 10, line 2, "such as tablets, injections, capsules" is indefinite because it is not clear if the physical forms are to be limited to these specific forms or not. It is suggested that the "such as" phrase could be deleted and made the subject matter of a further dependent claim. Claim 13 recites "significant analgesic activity with reduced dependence liability, respiratory depression, gastric irritation and sedation", but does not recite a standard with which it can be determined whether or not analgesic activity is significant and whether or not dependence liability, respiratory depression, gastric irritation and sedation are reduced. It is not clear if these results are based on a comparison with other prior art opioid peptides, or if they are based on a comparison with other formulations of the same opioid peptide recited in Applicants' claim.

4. Claims 2-4 and 6-14 are objected to because of the following informalities: At claim 2, line 1, "wherein" should be inserted after "claim 1". At claim 2, line 3, "and" should be inserted before "hydroxyethyl". At claim 3, line 2, and claim 6, line 2, the comma after "beta" should be deleted. At claim 4, line 2, "hydroxyethyl" is misspelled. At claim 6, line 2; claim 7, line 2; and claim 8, line 2; "glycyl" (first occurrence) is misspelled. At claim 8, line 3, "claim1" should be changed to "claim 1". At claim 10, line 2, a conjunction, e.g., "or" or "and", is needed before "capsules". At claim 11, line 3, "containing" is misspelled. At claim 12, line 1, "the" should be inserted after "wherein". At claim 12, line 2, "by a" should be inserted after "or". The claims would benefit from further grammatical revision. Appropriate correction is required.

5. Claims 13 and 14 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Note that claim 13 is dependent upon both claim 11 and claim 8, and that claim 14 is dependent upon both claim 11 and claim 1. See especially MPEP 608.01(I)(B)(3).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

7. Claims 1, 2, and 5-14 are rejected under 35 U.S.C. 103(a) as being obvious over the Nath et al article in view of Chiesi et al. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. The Nath et al article does not teach the opioid peptide in combination with a cyclodextrin derivative. Chiesi et al teach forming an inclusion complex of a basic drug and a cyclodextrin such as hydroxypropyl-β-cyclodextrin and dimethyl-β-cyclodextrin. The inclusion complex results in improved storage stability and enhanced water solubility and bioavailability for the drug. The drug is to be administered orally or parenterally.

See, e.g., column 3, lines 15-21; column 8, lines 54-56; and claim 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al in order to form inclusion complexes for pharmaceutical administration because the opioid peptide of the Nath et al article is a basic drug as required by Chiesi et al and because combining the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al would have been expected to increase the solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and cyclodextrin derivative in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

8. Claims 1-3, 7-11, and 13 are rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application '653 in view of the Nath et al article. The European Patent Application '653 teaches combining drugs, including peptide drugs such as enkephalins, with cyclodextrins, especially β-cyclodextrin. The combination permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs. See, e.g., column 1, lines 8-24; column 4, lines 4-11; and column 5, lines 31-36. The European Patent Application '653 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid

peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the European Patent Application '653 because the opioid peptide of the Nath et al article is a specific known example of the peptide and enkephalin drugs which are contemplated by the European Patent Application '653 and because administering the opioid peptide of Nath et al nasally in the pharmaceutical formulations of the European Patent Application '653 would avoid problems of poor absorption after oral administration and of undesirable metabolism as taught by the European Patent Application '653. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

9. Claims 1, 2, 4, and 7-14 are rejected under 35 U.S.C. 103(a) as being obvious over Hora et al in view of the Nath et al article. Hora et al teach combining polypeptide drugs with cyclodextrins, β-cyclodextrin, including hydroxyethyl-β-cyclodextrin. The combination improves the solubility and the stability of polypeptide drugs, and permits oral administration as well. See, e.g., the Abstract; column 10, lines 31-45, column 11, lines 59-64; column 16, lines 30-32 and 43; column 18, lines 45-49; and column 26, line 66 - column 27, line 4. Hora et al do not teach

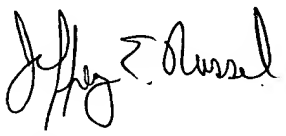
administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of Hora et al because the opioid peptide of the Nath et al article is a specific known example of the polypeptide drugs which are contemplated by Hora et al and because administering the opioid peptide of Nath et al in the pharmaceutical formulations of Hora et al would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

10. Claims 1, 7-13, and 15 are rejected under 35 U.S.C. 103(a) as being obvious over the French Patent '268 in view of the Nath et al article. The French Patent '268 teaches combining drugs, including analgesics and peptide hormones, with β-cyclodextrin. The combination permits the drugs to be administered transcutaneously. See the attached abstract. The French patent '268 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It

would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the French Patent '268 because the opioid peptide of the Nath et al article is a specific known example of the analgesic drugs which are contemplated by the French Patent '268, because the French Patent '268 would have been expected to be useful in transcutaneously administering polypeptides such as the opioid peptide of the Nath et al article because of the French Patent '268's disclosed ability to administer polypeptide hormones, and because administering the opioid peptide of Nath et al transcutaneously in the pharmaceutical formulations of the French Patent '268 would avoid problems of poor absorption after oral administration or of intrusive i.p. administration methods. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Christopher Low can be reached at (703) 308-2923. The fax number for Art Unit 1653 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 305-7401 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1653

JRussel

April 2, 2001